TUMORIGENISIS

No half measures, please

Protein phosphatase 2A (PP2A) is a serine–threonine phosphatase complex that contains three subunits. William C. Hahn and colleagues have found that mutations in the PP2A-Aα subunit contribute to human tumorigenesis by inducing functional haploinsufficiency.

The catalytic (C), regulatory (B) and structural (A) subunits of PP2A all have several isoforms. The mutant forms of the Aα-subunit that are found in human tumours are known to disrupt binding to the other subunits.

The authors tested the hypothesis that these mutant Aα-subunits exert a dominant effect by introducing them into a human cell line. Although the mutants disrupted the formation of the PP2A complex, which in turn reduced phosphatase activity, there was no increase in proliferation and no anchorage-independent growth or tumour formation.

The alternative hypothesis is that the non-functionality of these mutants causes tumorigenesis by reducing the levels of functional PP2A (haploinsufficiency). The authors used short hairpin RNAs (shRNAs) to reduce the expression of PP2A-Aα in the same cell line. They reduced expression by different amounts by increasing the titre of the shRNA. They found that reducing the amount of PP2A-Aα to approximately half of that found in wild-type cells caused an increase in proliferation, anchorage-independent growth and, when the cells were transplanted into immunodeficient mice, tumorigenesis. Interestingly, however, when the levels of PP2A-Aα were reduced further, the cells became apoptotic rather than proliferative.

In all cases in which the levels of PP2A-Aα were reduced, a decrease in the levels of the B-subunit and the C-subunit was also found, indicating that these are unstable when not bound to the A-subunit. Also, a reduction in Aα-subunits would make the B-subunit and C-subunit compete for A-subunits, with a consequent reduction in the number of certain types of complex. In particular, complexes that contained the B56γ-subunit were undetectable. Suppressing this subunit had previously been shown by the same authors to cause transformation.

Therefore, these findings add another link to our understanding of transformation and provide more evidence for the significance of haploinsufficiency as a mechanism in tumorigenesis.

Patrick Goymer

References and links

ORIGINAL RESEARCH PAPER Chen, W. *et al*. Cancer-associated PP2A Aα subunits induce functional haploinsufficiency and tumorigenicity. *Cancer Res.* **65**, 8183–8192 (2005)

WEB SITE

William C. Hahn's lab: http://research.dfci.harvard.edu/hahnlab

ANGIOGENESIS

Less restriction for TIE2

Bone marrow-derived cells have key roles in tumour angiogenesis. Luigi Naldini and colleagues have previously identified a subset of tumour-infiltrating cells that express the angiopoietin receptor TIE2 (TIE2-expressing monocytes, TEMs), and now show that TEMs are a distinct haematopoietic lineage of pro-angiogenic monocytes that are required for tumour blood-vessel formation.

The authors generated a transgenic mouse model that expressed green fluorescent protein (GFP) under the control of a lentiviral vector, which contained transcription-regulatory sequences of *Tie2*. Mouse mammary tumours (N202) that were grown subcutaneously in these mice expressed GFP in three cell populations: vascular endothelial cells ($TIE2^+$ $CD31^+$ $CD45^-$), haematopoietic TEMs ($TIE2^+$ $CD11b^+$ $CD45^+$) and a rare population of stromal cells ($TIE2^+$ $CD31^-$ $CD45^-$ $CD13^+$). When mice were made transgenic for thymidine kinase (TK) under the control of *Tie2*, and N202 tumours were established before treatment with ganciclovir to kill the TK-expressing cells, the tumours regressed with substantial endothelial cell apoptosis and further tumour growth was completely prevented. Haematopoietic stem cells, which also express TIE2, were not affected, as treated mice continued to have normal haematopoiesis; this suggests that the ganciclovir-sensitive TEMs were distinct from multipotent haematopoietic progenitor cells.

So, do these observations hold up in more clinically relevant models? The authors extended their findings to pancreatic tumours arising spontaneously in RIP1–Tag2 mice and human gliomas growing orthotopically in nude mice, all of which had been previously transplanted with *Tie2–GFP*-transduced bone marrow cells. They found that TIE2–GFP TEMs were present in the tumours and not in the surrounding tissues, that the TEMs expressed the potent pro-angiogenic molecule basic fibroblast growth factor, and that the tumours were highly vascularized. The TEMs (stained green in the figure) are a small fraction of the monocytes and macrophages infiltrating the tumour (blue) and often have a perivascular location, but do not express the CD31 marker of endothelial cells (red). Furthermore, if glioma cells were transplanted into nude mice with TIE2–TK bone marrow and then treated with ganciclovir to eliminate the TEMs, the tumours grew initially but then became avascular and regressed.

These data show that TEM activity accounted for most of the pro-angiogenic activity of bone marrow-derived cells that are recruited to tumours in the experimental models used. Therefore, TEMs might be key effectors of the angiogenic switch. A therapeutic strategy targeting all TIE2-expressing cells in tumours is worth further investigation.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER De Palma, M. *et al*. Tie2 identifies a hematopoietic lineage of proangiogenic monocytes required for tumor vessel formation and a mesenchymal population of pericyte progenitors. *Cancer Cell* **8**, 211–226 (2005)